REMARKS

Upon entry of the present amendments, claims 40, 42, 43, 57, 58, 63, and 71 to 73 will be pending in the application. Applicants have canceled non-elected claims 41, 52 to 56, 59 to 62, and 64 to 70 without prejudice as directed in the Final Office Action, and amended claims 58 and 71 to recite "providing a recombinant polypeptide". Support for these amendments can be found throughout the specification, e.g., at page 38, lines 5 to 11. The amendments add no new matter.

Although the amendments set forth above would add the new term "recombinant" to claims 58 and 71, they would raise no new issues that would require further consideration and/or search. The term to be added is well understood in the relevant field and is supported by the specification. Furthermore, it appears in a similar context in previously presented claims 40 and 73, so presumably has been examined already. Applicants submit that these amendments would place the claims into condition for allowance, or at least present the rejected claims in better form for consideration on appeal, and should therefore be entered after the final rejection under 37 C.F.R. § 1.116.

I. Information Disclosure Statement (IDS)

Applicants have not yet received an initialed copy of the IDS Form 1449 that was filed by applicants on May 7, 1999. Applicants request that the Examiner confirm that these references have been considered by returning an initialed copy of the Form to applicants as soon as possible.

II. Rejections under § 112, second paragraph

Claims 40, 42, 43, 57, 58, 63, and 71 to 73 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite due to applicants' use of the term "parathyroid hormone receptor." Applicants respectfully traverse for the reasons discussed below.

The Office Action states (at page 4, item 6):

> Applicants argue that Lindall et al. (US 4,508,828) understood what the term meant in 1983. However, Lindall et al. discussion of parathyroid hormone

> receptor is directed to a specific species of receptor found in a specific cell whereas the applicants' term "parathyroid hormone receptor" appears to have many different meanings. Page 36 of the specification provide several meaning of the term parathyroid receptor which can be the specific species, naturally occurring receptor, analog, fragment or amino acid substituted receptor which is not the ordinary and customary meaning disclosed in Lindall et al. It is not clear from the specification what is the metes and bounds of the claimed term.

Applicants acknowledge that their term "parathyroid hormone receptor" (PTH) is broad and includes a variety of parathyroid hormone receptor proteins. However, applicants respectfully submit that the claims should not be deemed indefinite simply because the term (and each claim as a whole) encompasses a large number of embodiments.

Applicants stated in their response to the previous Office Action, and reiterate here, that the term "parathyroid hormone receptor" is art-recognized and unambiguous. Applicants suggested that Lindall et al. (U.S. Patent No. 4,508,828; hereinafter "Lindall") appear to support applicants' position by referring to "PTH receptors" throughout their specification. Applicants submit, contrary to the Office Action's assertion, that Lindall does not appear to have used the term to describe "a specific species of receptor found in a specific cell." Rather, Lindall used the term as a generic description of an unidentified structure capable of binding parathyroid hormone and found in cultured animal tissue, cultured animal cells, and tissue extract (see, e.g., Lindall at column 3, lines 38 to 44). Although a preferred bioassay described in Lindall uses rat osteogenic cell cultures (which, according to Lindall, contain PTH receptors), Lindall makes clear (at column 12, lines 20 to 26) that other PTH receptor-containing materials can be used, such as "canine renal plasma membranes, human kidney cortical cell culture and other cultured animal tissue, cultured animal cells or tissue extract containing adenylate cyclase coupled PTH receptors." Thus, it appears that Lindall understood the term to include a wide variety of PTH receptors from many different animal species and cell types, and not just a single species of receptor found in a specific cell.

Applicants reiterate their position that the term is amply described and defined throughout the instant specification. For example, SEQ ID NOs: 18, 19, 20 and 21 are consistently referred to as "parathyroid hormone receptors" throughout the specification, e.g., at

page 36, lines 18 to 27, and at page 8, lines 1 to 18. The functions and structure of PTH receptors in general are also thoroughly described in the specification, e.g., at page 16, lines 7 to 17, page 27, line 1, to page 30, line 9, and at page 33, line 28 to page 34, line 4. Further, applicants have provided in the specification a drawing that shows a predicted arrangement of extracellular, intracellular, and transmembrane domains of a PTH receptor, thus illustrating pictorially what a full-length parathyroid hormone receptor looks like (see Fig. 21 and the specification at page 37, lines 14 to 16). Applicants submit that the term is well defined throughout the specification, and is therefore unambiguous.

For the reasons discussed above, applicants respectfully submit that the metes and bounds of the term are clear and request that the present rejection be reconsidered and withdrawn.

Claims 42 and 43 were rejected as allegedly indefinite due to applicants' use of the term "naturally occurring." The Office Action states (at pages 5 to 6, item 6):

> It is not clear when the receptor is naturally occurring or not and what is the naturally occurring receptor since depending on the definition of the term there may be several naturally occurring forms. Applicants argue that the claims have been amended to now clearly encompass fragments of non-recombinant proteins as well as polypeptides that are produced recombinantly. However, the claimed term is now even more confusing because it is not clear how a "naturally occurring" can be both be non-recombinant and recombinant receptors. It is not clear what is the metes and bounds of a receptor that is naturally occurring and non-naturally occurring.

As an initial matter, applicants wish to clarify certain statements that appeared in applicants' response to the previous Office Action (filed November 21, 2002), and that may have contributed to the Examiner's confusion. At page 7 of that response, applicants stated that scope of the amended claims "clearly encompasses fragments of non-recombinant proteins as well as polypeptides that are produced recombinantly." Similarly, at page 8, applicants stated, "the claims now unambiguously cover both polypeptides extracted from natural tissues and those produced by other means (e.g., recombinantly or by synthetic chemistry)." These statements are incorrect with respect to claims 40, 42, and 43 because part (a) of claim 40 recites "providing a

recombinant polypeptide," limiting the scope of the claims to the use of recombinant polypeptides. Applicants thank the Examiner for pointing out the discrepancy, and apologize for the confusion.

Based on the above-quoted language, applicants understand the Office Action to assert that applicants' use of the phrase "sequence of a fragment of a naturally occurring parathyroid hormone receptor" in claim 42 (and a similar phrase used in claim 43) is somehow inconsistent with the phrase "providing a recombinant polypeptide" recited in claim 40. Applicants respectfully disagree. Claims 42 and 43 make clear that the "naturally occurring" PTH receptor recited in both claims is merely a reference sequence, i.e., a sequence to which the sequence of the recombinant polypeptide provided in part (a) of claim 40 is compared, not the actual molecule to be used in the recited methods. As such, the Office's concern that the claims are potentially confusing is unwarranted because the claims do not characterize the recombinant polypeptide as a "naturally occurring" polypeptide. Accordingly, applicants submit that the metes and bounds of the claims are clear, and request that the present rejection be reconsidered and withdrawn.

Claims 40, 42, 43, 57, 58, 63, and 71 to 73 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for missing an "essential step." The Office Action states (at pages 4 to 5, item 6):

> The omitted steps do not fulfill the preamble stated purpose of identifying a compound that inhibits binding of a parathyroid hormone to a parathyroid hormone receptor. The method step set forth for competition while identifying a compound which may compete does not identify a compound which inhibits. Competitive binding and inhibition binding have a separate meaning in the art. For example in any binding methods the determination of non-specific binding and determination of specific binding is important because the method assays are in an equilibrium. In the equilibrium if the control assay and the compound testing assay have different receptor concentration or ligand concentration or compound concentration then the specific binding cannot be determined to be competitive or inhibitory. Furthermore, if the test compound is a protease while it modulates competitive binding is not inhibiting binding since the effect is not related to the affinity of the receptor for ligand or the test compound. A

> relationship between the specific binding of the competitive binding has to be established with the inhibition of binding.

Applicants are not sure what the Examiner is suggesting here. Based on the above-quoted paragraph, applicants believe the Office's position is that the claims are indefinite because they do not recite performing experimental controls to account for falsely positive results due, for example, to non-specific binding or damage to the PTH receptor caused by a test compound. Applicants respectfully traverse this rejection because such controls are not essential elements of the invention. While the use of such controls may optimize the results obtained in the assay, e.g., by reducing "false positives," they are not a required aspect of the invention.

Applicants submit that whether and what type of experimental controls should be performed will vary depending upon how the assays themselves are to be performed. The assay would normally be set up to minimize false positives such as in the Examiner's "protease" example. It could very well have a lot of other aspects that are not, and should not be, recited in the claim: e.g., details concerning the binding readout methodology. Further, the assay may be set up so that the controls are not repeated every time the assay is performed, so that requiring inclusion of a control step in the claim would be unduly limiting.

The purpose of a patent claim is not to set out complete, step-by-step instructions for carrying out an assay, as in a laboratory protocol. Rather, the claim should indicate the steps that distinguish the claimed method from all prior art methods. One of ordinary skill could choose to add steps, including control steps, or not. Here, applicants are not relying on any particular control step to distinguish over prior art. Thus, applicants submit that the claims are not missing essential steps and request that the present rejection be reconsidered and withdrawn.

III. Rejections under 35 U.S.C. § 112, first paragraph

Claims 40, 42, 43, 57, 72,and 73 were rejected as allegedly adding new matter. The Office Action states (at page 6, item 7):

> The newly amended claim 40 and new claim 73 encompass the subgeneric invention which is a combination method of competition and inhibition binding of a test compound. However, the original claim 40 was drawn to competition and

> the original claims 58 and 71 are drawn to inhibition binding, while the specification does not disclose a method of using a combination of competition and inhibition.

Based on the above-quoted paragraph, applicants believe the Office's position is that claims 40 and 73, which recite "identifying a compound that inhibits binding of a parathyroid hormone to a parathyroid hormone receptor by competitively binding to the parathyroid hormone receptor," somehow includes matter that was not disclosed in the application as originally filed. Applicants respectfully disagree and traverse this rejection. Applicants submit that "competitive binding" is a type of "binding." A complete description of binding, including competitive and non-competitive binding, is provided, for example, in the specification at page 45, lines 1 to 16. It is clear that the concept of screening for compounds that inhibit binding by competitively binding was explicitly contemplated by the original specification. Accordingly, claims 40 and 73 (and claims 42, 43, 57, and 72) add no new matter to the application. Applicants request that the present rejection be reconsidered and withdrawn.

Claims 40, 42, 43, 57, 58, 63, and 71 to 73 were rejected as allegedly lacking written description. Applicants respectfully traverse this rejection for the reasons discussed below.

The Office Action states (at page 7, item 8):

> Applicants argue that the amendment to claim 40 with regard to "naturally occurring" term which was also discussed above with regard to 35 USC 112, second paragraph, now unambiguously cover both polypeptides extracted from natural tissues and those produced by other means. However, as discussed above it is not clear what is the metes and bounds of a receptor that is naturally occurring and non-naturally occurring. The large genus of molecules which encompass the term is not adequately described in the specification.

As applicants discussed in their response to the previous Office Action, Examiner Eyler indicated (during an interview on September 18, 2002) that the present rejection under 35 U.S.C. § 112, first paragraph, is related to the rejection of the claims under 35 U.S.C. § 112, second paragraph, for use of the term "naturally occurring." To address the Office's concerns, applicants amended claims 42 and 43 in their previous response to clarify that the methods

require providing a recombinant polypeptide that includes an amino acid sequence that is identical to the sequence of a fragment of a naturally occurring PTH receptor. Claims 42 and 43 make clear that the "naturally occurring" PTH receptor recited in both claims is a "reference sequence," and not the actual molecule to be used in the recited methods. Thus, the Office's concerns regarding "the metes and bounds of a receptor that is naturally occurring and non-naturally occurring" are unwarranted.

Further, applicants maintain their position that they satisfy the written description requirement for use of the full genus of PTH receptors through a description of a representative number of PTH receptor species, as well as by disclosure of relevant, identifying characteristics of the PTH receptors, e.g., structural and chemical properties (see the MPEP at §2163(II)(A)(3)(a)(ii)). The PTH receptors described in the specification (e.g., by providing nucleic acid and amino acid sequences) are representative of the entire genus of PTH receptors, and a sufficient variety of species is described to reflect the variation within the genus. Applicants have described the cloning and identification of four PTH receptors isolated from three distantly related mammals, including a rodent (rat), a marsupial (opossum), and a human. Experiments described in the specification show that the sequences of the PTH receptors are highly conserved and provide evidence that there is relatively little variation within the genus of PTH receptors. Thus, the facts of the present situation are not the same as those in the *University of California v. Eli Lilly and Co.* case cited in the Office Action, and in fact are much more favorable to applicants than in the cited case.

Finally, applicants note that the Office Action includes dependent claims 57, 63, and 72 in the present rejection. Applicants believe this was in error, as each of these claims recites a specific sequence, SEQ ID NO: 21.

For the reasons discussed above, applicants submit that the claims comply fully with the written description requirement. Accordingly, applicants request that the present rejection be reconsidered and withdrawn.

Claims 40, 42, 43, 57, 58, 63, and 71 to 73 were rejected as allegedly not enabled. Applicants respectfully traverse this rejection.

The Examiner acknowledges (at page 8 of the Office Action) that the specification is "enabling for a method of using the receptor which comprises the structural domain which binds the PTH", but opines that the specification "does not enable a method of using a PTH receptor which comprises any six amino acids to any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims." Applicants remind the Examiner that the claims are explicitly limited to use of fragments that do bind to PTH, and do not encompass use of "any six amino acids," as the Examiner fears. The only fragments that can be used in the methods of claim 40, 42, 43, 57, 58, 63, and 71 to 73 are fragments that bind PTH. So by definition, every such fragment must comprise a structure that permits it to bind PTH, a scope that the Examiner acknowledges is adequately enabled by the specification.

Applicants reiterate their position that it is well within a skilled practitioner's abilities to determine which fragments of a PTH receptor can bind to PTH, especially in view of the detailed information provided in the specification. For example, the specification discloses the full nucleic acid and amino acid sequences of 4 different PTH receptors, and provides a figure illustrating a predicted arrangement of extracellular, intracellular, and transmembrane domains of a PTH receptor (see Fig. 21). Also disclosed at page 37 are the amino acid sequences of the extracellular and intracellular domains of the rat bone PTH receptor (SEQ ID NOs:5 to 13). These domains were synthesized and purified by the applicants (see page 37, line 17, to page 38, line 3), and range in length from 10 to 25 amino acid residues. The specification also teaches that the sequences of PTH receptors are highly conserved, allowing data from PTH receptors described in the specification to be extrapolated to PTH receptors from other species (page 23, lines 25 to 30). Applicants submit that with such detailed information, a skilled practitioner would know the structure of any PTH receptor and could easily determine which fragments bind to PTH through routine and predictable experimentation.

Applicants submit that the Office's concerns are unwarranted in view of the functional limitations in the claims, and in view of the skilled practitioners' abilities to determine which fragments of a PTH receptor can bind to PTH. Thus, applicants request that the present rejection be reconsidered and withdrawn.

IV. Rejection under 35 U.S.C. § 102

Claims 58, 63, and 71 were rejected as allegedly anticipated by Lindall et al. (U.S. Patent No. 4,508,828). The Office Action states (at page 11, item 10):

> Applicants argue that Lindall et al. does not describe the use of recombinant polypeptide. Claim 40 and its dependent claims have overcome the rejection. However, the rejoined claims 58, 63, and 71 do not recite newly amended claim limitation "recombinant polypeptide".

In the interest of moving the present application toward allowance, applicants have amended independent claims 58 and 71 to recite "providing a recombinant polypeptide." Applicants respectfully request that the present rejection be withdrawn.

CONCLUSION

Applicants respectfully request that the proposed amendments be entered and that all claims be allowed. Enclosed is a check for $420 for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 00786-071005.

Respectfully submitted,

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REG. NO. 54,112

Janis K. Fraser, ~~Ph.D.~~, J.D.
Reg. No. 34,819

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

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